Scientific Abstract:

Cancers of the colon and rectum are the second leading cause of cancer death in the United States and the colon and rectum are the third and fourth most common sites of malignancy in most Western countries. It is estimated that there will be nearly 135,000 new cases of colorectal cancer diagnosed in the United States and this rate has been increasing by approximately 5% each year (1). Rectal cancers present a particular challenge for local control given the anatomic considerations of the pelvis and their propensity to invade radially.

In this protocol, we will combine TNFerade™, an adenoviral gene transfer vector that expresses TNF-α, an anti-cancer protein, with preoperative chemoradiation (oral capecitabine at 900mg/m^2 BID and 45 Gy plus 5.4-9.0 Gy boost of radiation). TNFerade™ contains the EGR-1 promoter ligated upstream from the TNF-α gene so that the TNF-α protein is produced at the site of the cancer. A practical aspect of this design is that expression of TNF-α can be spatially localized to injected and radiated tissue, thereby minimizing the risk of systemic toxicity. The goal of therapy is to allow for the complete resection of these tumors while preserving sphincter function whenever possible.

The population for this study will be newly diagnosed adult subjects with locally advanced rectal cancer (stage T3 and T4) limited to the rectum and regional lymph nodes who have not received prior treatment and are to receive chemoradiation prior to surgery. Patients with metastatic disease at time of screening are not eligible.

Combinations of pre-operative radiation and 5-FU based chemotherapy followed by surgery result in complete pathologic responses in roughly 10-25% of cases. This trial is designed to determine if the local injection of a replication incompetent adenoviral vector carrying a radiation inducible TNF construct followed by radiation and chemotherapy can improve the complete pathologic response rate when compared to radiation and chemotherapy alone at the time of definitive surgical resection of locally advanced rectal cancers. The initial phase of the study will be a feasibility stage in which up to 10 patients will be enrolled. If complete pathological response is not observed in 3 or more patients, the randomized phase of the study will be abandoned because the upper bound of a one-sided 90% confidence interval about 2/10 is 45%, and thus it is not likely that the TNFerade + chemoradiation is doing sufficiently better than chemoradiation alone in order to be able to detect it in the randomized portion of the trial assuming that the rate of pathologic complete response with chemoradiation alone is 25%. The randomized phase will consist of a 1:1:1 randomization to one of two doses of TNFerade (4 x 10^9 and 4 x 10^{10} pu) + chemoradiation versus chemoradiation alone. An evaluation of futility will be conducted in this portion of the study also once 13 patients have been enrolled in each arm. Secondary endpoints will include disease free and overall survival as well as measurements of local and systemic gene product levels and determinations of changes in gene expression profiles as well as proteomic analysis of tumor tissue prior to, during and following therapy.

(1) Jemal, A., Thomas, A., Murray, T., and Thun, M. Cancer statistics, 2002. CA Cancer J Clin, *52:* 23-47, 2002.